Diplomarbeit

Cerebral Magnetic Resonance Imaging for Assessment of Microembolic Cerebral Lesions after Percutaneous Aortic Valve Replacement

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Graz, am

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

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Abstract

Purpose: Aortic stenosis (AS) is currently the most frequent acquired heart valve disease in the western world. In symptomatic patients with severe AS, operative aortic valve replacement is the treatment of choice. However, not only symptomatic AS becomes more prevalent in elderly patients, but also comorbidities that increase the risk of operative valve replacement. For this subgroup of patients percutaneous aortic valve replacement (PAVR) is an emerging less invasive treatment option. While embolic stroke is a well-known complication of PAVR, this study aimed to assess frequency and extent of subclinical microembolic cerebral lesions after PAVR.

Patients and methods: In our institution, 46 patients (15 male, 31 female; mean age 81 ± 5 years) with symptomatic severe AS underwent PAVR between July 2008 and November 2009. The self-expanding CoreValve prosthesis was implanted via transfemoral access using the current 18 French delivery catheter system. 37 patients were scheduled for cerebral diffusion-weighted magnetic resonance imaging (DW MRI) two days before and up to six days after PAVR. Nine patients were not eligible due to pacemaker implantation prior to enrolment. 25 patients underwent both pre- and postinterventional DW MRI, while twelve patients could not undergo postinterventional MRI and had to be excluded from analysis (need for permanent pacemaker implantation, n=2; critical status, n=5; MRI not available, n=5).

Results: Thorough physical examination did not reveal any changes in neurological status after PAVR. However, comparison of pre- and postinterventional DW MRI showed that 23 of 25 patients (92%) had newly acquired bright lesions ($p < 0.001$) in accordance with subclinical cerebral embolisation: class I (1-3 new bright lesions), n=9 (36%); class II (4-7 new bright lesions), n= 8 (32%); class III (≥8 new bright lesions or cortical infarction), n=6 (24%). Only in two patients (8%) there was no evidence for any newly acquired bright lesion (class 0).

Conclusion: PAVR with the self-expanding CoreValve bioprosthesis is an emerging alternative treatment option for high-risk patients with symptomatic severe AS. Albeit risk of stroke is low, the vast majority of patients show newly acquired bright lesions in DW MRI compatible with subclinical cerebral embolisation.

Zusammenfassung

Einleitung: Die Aortenstenose (AS) ist die häufigste Ursache für erworbene Herzfehler in der westlichen Welt. Der operative Aortenklappenersatz ist für symptomatische Patienten die Therapie der Wahl. Es steigt jedoch nicht nur die Häufigkeit der AS in der älteren Bevölkerung sondern auch Begleiterkrankungen, die das operative Risiko drastisch erhöhen. Für diese Patientengruppe ist der perkutane Aortenklappenersatz eine wenig invasive Behandlungsmöglichkeit. Der embolische Schlaganfall ist eine bekannte Komplikation der PAVR. Das Ziel dieser Studie war jedoch die Frequenz und das Ausmaß von subklinischen mikroembolischen cerebralen Läsionen nach der PAVR zu erfassen.

Material und Methoden: In unserem Institut wurden 46 Patienten (15 m, 31 w; mittleres Alter 81 ± 5 Jahre) mit hochgradiger symptomatischer AS mit einer PAVR im Zeitraum von Juli 2008 bis November 2009 versorgt. Die selbstexpandierende CoreValve Prothese wurde über einen transfemoralen Zugang mit dem 18 French Implantationskathetersystem eingebracht und freigesetzt. 37 Patienten waren für eine diffusionsgewichtete Schädel Magnetresonanztomographie (DW MRI) zwei Tage vor und bis zu sechs Tage nach der Intervention vorgesehen. Neun Patienten wurden aufgrund eines vorhandenen Schrittmachers (SM) aus der Studie ausgeschlossen. 25 Patienten erhielten ein pre und postinterventionelles DW MRI. Zwölf Patienten erhielten kein postinterventionelles DW MRI und wurden aus der Analyse exkludiert (SM Indikation nach PAVR, n=2; kritischer Status, n=5; MRI nicht verfügbar, n=5).

Ergebnisse: Gründliche neurologische Statuserhebung zeigte keine Veränderungen nach der PAVR. Die Auswertung der pre und postinterventionellen DW MRI Aufnahmen zeigte jedoch, dass 23 von 25 Patienten (92%) neu aufgetretene helle Läsionen hatten ($p < 0.001$), welche mit subklinischen Mikroembolisationen vereinbar sind: Klasse I (1-3 neuaufgetretene Läsionen), n=9 (36%); Klasse II (4-7 neuaufgetretene Läsionen), n=8 (32%); Klasse II (>8 neuaufgetretene Läsionen), n=6 (24%). Nur bei zwei Patienten (8%) konnten keine radiologischen Veränderungen festgestellt werden (Klasse 0).

Diskussion: PAVR mit der CoreValve Prothese ist eine alternative Behandlungsmöglichkeit für Hochrisikopatienten mit einer hochgradigen symptomatischen AS. Obgleich das Risiko eines Schlaganfalles gering ist, zeigt die große Mehrzahl der Patienten (92%) im DW MRI neuaufgetretene helle Läsionen, die mit subklinischen cerebralen Embolisationen vereinbar sind.

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Aortic stenosis

Introduction

According to the euro heart survey on valvular heart diseases aortic stenosis (AS) is the most frequent valvular heart disease in our times. Roughly 43% of all patients with valvular heart disease present themselves under the condition of an aortic stenosis. In general the aortic stenosis is a disease of the older age. Patients often combine different cardiovascular risk factors and comorbidities. (1)

Through the last decades the main cause of aortic stenosis has shifted, via improved medical care, better life standards, the widespread use of antibiotics and the generally elevated life expectancy in the western world from the post inflammatory rheumatic origin to the degenerative (senile) calcification of the aortic cusps.

Definition

Aortic stenosis is usually defined by restricted systolic opening of the valve leaflets and is the most common cause of a left ventricular outflow obstruction.

According to the guidelines on the management of valvular heart disease of European Society of Cardiology, the classification of the aortic stenosis is rather simple: a valve area < 1.0 cm² or indexing to body surface area (BSA) the cut-off value < 0.6 cm²/ m² is considered as severe aortic stenosis. Furthermore severe stenosis is unlikely if cardiac output is normal and there is a mean pressure gradient <50 mmHg. (2)

The American Heart Association classifies the aortic stenosis in its guidelines for the management of patients with valvular heart disease as follows:

Classification Aortic Stenosis AHA Guidelines			
Indicator	Mild	Moderate	Severe
Jet velocity (m/s)	< 3.0	3.0 – 4.0	> 4.0
Mean gradient (mmHg)	< 25	25 – 40	> 40
Valve area (cm²)	> 1.5	1.0 – 1.5	< 1.0
Valve area index (cm² per m²)			< 0.6

Table 1 Classification of aortic stenosis according to the AHA guidelines (3)

Epidemiology

According to the Euro Heart Survey, a multicenter study with a sample of 5001 patients conducted in the year 2001, aortic stenosis was the most frequent valvular heart disease (1197 patients, 43.1%), followed by mitral regurgitation (877 patients, 31.5%), aortic regurgitation (369 patients, 13.3%), and mitral stenosis (336 patients, 12.1%). (1)

Interpreting the data from the american population based study "Burden of valvular heart diseases" (11911 echocardiographicly analyzed patients) the prevalence of valvular heart disease is rising with advanced age (18–44 years 0.7%, 45–54 years 0.4%, 55–64 years 1.9%, 65–74 years 8.5%, ≥75 years 13.2%).
The most frequent origin of valvular heart disease in the age group of 75 and older is mitral regurgitation, with a prevalence of 9.3%, followed by aortic stenosis with a prevalence of 2.8%. (4)

Overall aortic stenosis is a disease of the elderly except for patients with an unicuspid or bicuspid aortic valve (5; 6) with a slightly higher prevalence in men. (4)
Summing up, about 25% of people older than 65 in western populations, feature aortic sclerosis, and 3% older than 75 severe stenosis. (6)

Etiology

Aortic stenosis in adults may be due to degenerative calcification of the aortic cusps, caused either by congenital configuration or secondary succeeding a rheumatic inflammation.

Nowadays, at least in the western world, degenerative etiology is by far the most frequent in aortic stenosis (1197 patients, degenerative 81.9%, rheumatic 11.2%, congenital 5.4%, endocarditis 0.8%, inflammatory 0.1%, other 0.6%). (1)

A combination of different factors and lifestyle improvements have been postulated to explain the considerable decrease in the rheumatic origin of aortic stenosis: improved living standards, better access to health care, wider use of antibiotics, as well as natural changes in virulence of the rheumatic streptococcal strains, et cetera. (7)

Age related degenerative calcific aortic stenosis (senile or sclerocalcific aortic stenosis)

Over the last years different studies suggest that calcific aortic valve stenosis is rather an active than a passive biological process within the valve leaflet, causing regulated bone formation promoted through inflammation and extra cellular matrix remodeling. (8)

Risk factors shared by atherosclerosis and aortic stenosis, such as age, male gender, smoking, diabetes mellitus, hypertension, increased low density lipoproteins (LDL) and reduced high density lipoproteins (HDL) - cholesterol, strongly suggest that a similar process underlies the development and progression of both diseases. (9)

The histological changes of calcific aortic stenosis are inflammation, extracellular matrix remodeling with increasing fibrosis, valve thickening, as well as angiogenesis and calcification. In a possible pathogenetic concept the high mechanical stress on the aortic valve, together with atherosclerotic risk factors, leads to valvular endothelial dysfunction/leakage, followed by deposition of LDL particles as well as other compounds, which trigger inflammation. That in turn activates valvular interstitial cells (VICs) resulting in their osteoblastic transformation. (8)

<u>Valve Interstitial Cell Transformation</u>

Valvular interstitial cells (VICs) are the most prevalent cells in the heart valve and are found in all 3 layers of the valve: the fibrosa, the spongiosa, and the ventricularis. 5 phenotypes exist they are thought to be responsible for maintaining the structural integrity of the valve. For the pathogenetic process at the heart valve 3 phenotypes seem to be relevant: the quiescent valvular interstitial cells (qVICs), which maintain physiologic valve structure as well as function and inhibit angiogenesis in the leaflets. The osteoblastic valvular interstitial cells (obVICs), which are responsible for calcification, chondrogenesis and osteogenesis in the heart valve by secretion of alkaline phosphatase, osteocalcin, osteopontin and bone sialoprotein and the activated valvular interstitial cells (aVICs), which possess repairing capabilities.

The aVICs subpopulation is positive for alpha-smooth muscle actin (αSMA) and thus is referred to as myofibroblasts. These myofibroblasts respond to valve injury attributable to pathological conditions as well as abnormal hemodynamic/mechanical forces with activated cellular repair processes including proliferation, migration and matrix remodeling. qVICs become aVICs under conditions of pathological injury or abnormal hemodynamic/mechanical stress. This is usually associated with increased extracellular matrix (ECM) secretion and

degradation, expression of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs), as well as increased proliferation and migration. Furthermore, activated valvular interstitial cells also increase secretion of cytokines, one of the most important being transforming growth factor β (TGF-β), which promotes the differentiation into osteoblastic valvular interstitial cells (obVICs). After completion of remodeling, many aVICs are eliminated by apoptosis. When dysregulation of this process occurs, aVICs persist with continued force generation. Dysfunction of apoptosis, in combination with abnormal extracellular matrix production and remodeling may result in pathological fibrosis, angiogenesis, chronic inflammation and calcification, giving rise to clinical valve diseases. (10)

Inflammation

Cellular inflammatory infiltrates are not typical in normal aortic valve tissue. Scattered macrophages, possibly increasing with advanced age, and mast cells, but no lymphocytes, are present in normal aortic valves.

In contrast, cells morphologically resembling monocytes macrophages and T lymphocytes can be found in calcified valves. Monocytes at the calcification front are secreting non-collagenous matrix proteins (NMPs), whereas T lymphocytes are often in the vicinity of macrophages consistent with their regulatory role. The precise function of these leukocytes remains uncertain, though.

Interestingly, toll-like receptors and the complement system seem also to be involved in the pathogenesis of calcific aortic valve stenosis, as in vitro stimulation of toll-like receptors can lead to an osteoblastic phenotype of valvular interstitial cells. (8)

Angiogenesis

Endothelial dysfunction is another element associated with degenerative aortic stenosis. A study which compared 30 stenotic valves with 20 normal aortic valves, revealed that the degenerated valves contained blood vessels in specific areas in contrast to the normal valves, which were completely avascular. (11)

Angiogenetic factors found in heart valves are vascular endothelial growth factor A (VEGF-A), its receptors vascular endothelial growth factor receptor 1/2 (VEGF R-1/2), and tyrosine kinase with immunoglobulin-like and EGF-like domains-2 (Tie-2). These factors are synthesized by stromal cells and leukocytes. Antiangiogenetic factors in heart valves are

chondromodulin-I, endostatin, and osteonectin (secreted protein, acidic and rich in cysteine = SPARC). (8; 12; 13)

Extracellular matrix remodeling

During later stages, aortic valves show extensive thickening and matrix remodeling, which are attributed to increased cell proliferation, matrix synthesis, and the expression and activation of matrix metalloproteinases (MMPs) produced through inflammatory cells. (14; 15)

Matrix metalloproteinases are a family of 23 zinc-dependent endopeptidases that are involved in almost all physiologic and pathologic processes of tissue remodeling. Activation of matrix metalloproteinases on extracellular matrix remodeling increases space for cell migration (e.g. tumor cells), activates or sets free signaling molecules (e.g. TGF-β), deactivates signaling molecules (e.g. CXCL-12), and degrades cell-adhesion molecules (e.g. desmoglein-1) as well as basement membranes. (16)

The source of matrix metalloproteinases are valvular interstitial cells (VICs), monocytes-macrophages, lymphocytes and endothelial cells. (11; 14; 15) TIMPs (tissue inhibitors of metalloproteinase) are the endogenous inhibitors of matrix metalloproteinases which, apart from MMP inhibition, may exert further effects on cell differentiation and proliferation. Interestingly, each valve has a certain pattern of TIMPs. (17)

Biomineralisation

Heterotopic ossification occurs commonly in end-stage valvular heart disease and presents with features of active bone remodeling leading to osteoblastic bone formation and osteoclastic bone resorption, including microfractures and hematopoetic tissue. (18)

Presumably this process is mediated by non-collagenous matrix proteins (NMPs) which are increasingly secreted by leukocytes and valvular interstitial cells under stress (11; 14; 15).

Signaling pathways such as Wnt signaling (19), the angiotensin and kinin system (20) or the OPG/RANKL/RANK system (21) stimulate valvular interstitial cells to undergo osteoblastic differentiation (obVIC) promoting calcification. An increase in alkaline phosphatase, which is essential for nodule formation and calcification, in noncollagenous matrix proteins, such as osteopontin or osteocalcin, and in Runx2 are mostly late markers of osteoblast differentiation expressed during active mineralization. (10; 22; 23) These proteins are upregulated by valvular interstitial cells, monocytes-macrophages, and probably T-lymphocytes in calcific aortic stenosis.

Non-collagenous matrix proteins (NMPs) act as regulators of biomineralisation and pursue no structural role unlike the fibrillar extracellular matrix proteins (e.g. collagen). Osteocalcin (BPG) is chemoactive for monocytes and mesenchymal cells. γ-carboxyglutamic acid protein (MGP), protects non-osseous tissue from calcification. Osteonectin (SPARC) inhibits angiogenesis, matrix metalloproteinases (MMPs) and induces apoptosis. Osteopontin acts as an inhibitor of tissue calcification. Bone sialoprotein is crucial for the nucleation of hydroxyapatite. (8)

Fetuin-A, a member of the cystatin superfamily of cysteine protease inhibitors, is a negative acute-phase protein that has been identified as a potent circulating inhibitor of the calcification process. Fetuin-A perturbs hydroxyapatite formation by reducing crystal formation. It can also assemble a high molecular mass complex with calcium phosphate mineral and matrix γ-carboxyglutamic acid protein (MGP), a key regulator of tissue calcification. Furthermore, it has been shown to antagonize osteogenic growth and differentiation factors, to control bone metabolism, to play a basic role in phagocytosis regulation and, finally, to mediate vascular smooth muscle cell (VSMC) calcification. Elevated fetuin-A concentrations have been observed more frequently in calcified than in native valves presumably as an effort to stop the progress of calcification. (24)

There is evidence that the runt-related transcription factor 2 (Runx2, Cbfa-1) is the downstream target of several of the identified cellular pathways upregulated in calcific aortic stenosis. Runx2 is a master regulator of bone development, and essential for differentiation of mesenchymal stem cells to osteoblasts. Runx2 was shown to be increased in stenotic valves. In vitro stimulation of primary cultures of aortic valvular interstitial cells (VICs) with TNF-α and the TNF-α family member RANK Ligand leads to an enhanced DNA-binding of Runx2 indicating Runx2 binding to its promotors. Some of these mechanisms interact and work cooperatively in skeletal bone formation. Runx2 may serve as a signal integration point of these cytokine families. (8)

Rheumatic endocarditis of the aortic leaflets

The pathogenesis of rheumatic fever in susceptible individuals is related to autoimmune humoral and cellular responses directed towards human tissue, triggered by the response to Streptococcus pyogenes. Arthritis is one of the earliest and most common features of the disease, present in 60% to 80% of patients. Carditis, the most serious manifestation of the disease, affects 30% to 45% of rheumatic fever patients and causes heart damage mainly in the valves, leading to rheumatic heart disease.

Group A streptococci, like Streptococcus pyogenes, contain M, T and R surface proteins and lipoteichoic acid (LTA), involved in bacterial adherence to pharyngeal epithelial cells. The M protein is the most important antigenic structure of the bacterium and shares structural homology with alphahelical coiled-coil human proteins such as cardiac myosin, tropomyosin, keratin, laminin, vimentin and several valvular proteins.

The molecular mimicry mechanism is responsible for the cross-reactions between streptococcal antigens and human proteins, especially heart tissue proteins, in susceptible individuals. Humoral and cellular immune responses are involved in the development of rheumatic fever autoimmune reactions. It is now known that rheumatic heart disease lesions are mediated mainly by $CD4^+$ T cells. These T cells show a degenerated pattern of antigen recognition (streptococcal antigens and autoantigens). The lack of IL-4, a regulatory cytokine, in the valvular tissue is involved in the progression and permanence of these lesions. In addition, the lack of IL-4 probably perpetuates and/or exacerbates the production of inflammatory cytokines (TNF-α and IFN-γ). The ongoing rheumatic process produces commissural fusion, sometimes resulting in a bicuspid valve, making the leaflets more susceptible to trauma and ultimately leading to fibrosis, calcification and further narrowing. (25–28)

Congenitally affected valve

The congenitally affected valve may be stenotic at birth and become progressively more fibrotic, calcified and stenotic. A decreased number of cusps is associated with male gender, younger patient age at surgery and an increased occurrence of pathological changes in the cusps, including calcification of both the cusp and the base, ossification and ulceration. (5; 29)

The normal tricuspid aortic valve and the congenitaly bicuspid aortic valve depend on folding to fulfill their function. The physiologicaly functioning tricuspid aortic valve unfurls in full opening as well as in full closure. Thus allowing the valve to evade the systolic pressure load completely, and allowing it to receive the diastolic pressure load in a ready state with its cusps smooth, fully extended, and in a linear approximation, when diastole occurs. However, the congenital bicuspid aortic valve is congenitally stenotic, thus unable to escape the systolic pressure load, as well as having to receive the diastolic pressure load in an unprepared folded state.

To allow wrinkle-free coaptation of the normal tricuspid aortic valve during diastole, as well as full opening during systole, the total length of the free edges equals the circumference and exceeds that of the intercommissural distances.

The congenital bicuspidy aortic valve however shows a leaflet length discrepancy between full opening and full closure, which is compensated through several mechanisms. Increased bulging of the leaflet domes extends the area of approximation of the cusps where they touch their counterparts or asymmetrical approximation, where the cusps make contact laterally of the midline. Therefore gradual folding and unfolding is not only excessive, but some folds and creases persist throughout the cardiac cycle. Additional turbulence may induce further irregularities of the opening-closure mechanism through whipping and trembling, predisposing it to fibrosis and calcification

Thus the diastolic pressure stress and the far more complex mechanical stress of leaflet flexion, contact, folding and creasing are leads to an abnormally high stress with the first heartbeat, accountable for the earlier development of degenerative aortic valve disease in patients with congenitaly bicuspid aortic valve. (30)

Pathophysiology

In adults with aortic stenosis, the obstruction develops gradually, usually over decades. Nonetheless, the obstruction to left ventricular outflow produces a systolic pressure gradient between left ventricle and aorta. Continuously elevated pressure leads to increased left ventricular afterload and therefore to persistent wall stress. The left ventricle responds by initial dilatation followed by gradual wall thickening and consequent reduction of the afterload (which is generally quantified as wall stress) to near a physiological level, thus maintaining a normal normal ejection fraction and stroke volume. After successful adaptation to the pressure overload, hypertrophy per se did not cause an intrinsic depression of the myocardial inotropic state. (31–33)

The Laplace equation can be used as illustration:

$$\sigma = p \cdot r / 2 \cdot th$$

Wall stress (σ) $\triangleq$ afterload, p is left-ventricular pressure, r is left-ventricular radius, and th is left-ventricular thickness.

As pressure grows in the numerator of this equation it is offset by a rise in wall thickness (concentric left-ventricular hypertrophy) in the denominator, keeping afterload (wall stress) normal. (33)

The concentric hypertrophy is characterized by a reduced end-diastolic-radius to wall-thickness ratio with an essentially normal cavity shape. As long as the product of end-diastolic-radius to wall-thickness ratio and left ventricular systolic pressure remains constant, hypertrophy is appropriate. Usually the resulting increase in relative wall thickness is enough to counter the high intracavitary systolic pressure and, as a result, left ventricular systolic wall stress remains within the physiological range. As long as the wall stress is kept normal, the ejection fraction is preserved, due to the inverse relation between systolic wall stress and ejection fraction.
However, if the hypertrophic process is inadequate and relative wall thickness does not increase in proportion to pressure (characterized through an increase of the product of end-diastolic-radius to wall-thickness ratio and left ventricular systolic pressure signaling an increase in wall stress), the ejection fraction decreases as a consequence of the elevated afterload. (34; 35)

Another factor decreasing the ejection fraction is a depressed contractile state of the myocardium. (36).

As a result of the concentric hypertrophy and the structural changes of the left ventricular myocardium, such as an increased wall thickness, low volume/mass ratio and reduced compliance of the chamber, due to increase of myocardial stiffness, the left ventricular end-diastolic pressure increases without chamber dilatation. The increased end-diastolic pressure primarily reflects the diastolic dysfunction. (37–39)

Atrial contraction plays a particularly important role in the filling of the left ventricle in aortic stenosis. Stott et al. (40) observed in a study conducted in 1971, that the forceful left atrial forward stroke volume contributed 39% of the volume ejected during ventricular systole for the aortic stenosis group whereas in the control group it represented 26% of the stroke volume. Additionally it raised the left ventricular end-diastolic pressure to the elevated level necessary for effective left ventricular contraction without increasing mean left atrial or pulmonary venous pressure, therefore preventing pulmonary congestion. Loss of properly timed atrial contraction occuring with atrial fibrillation or atrioventricular dissociation, is often followed by serious clinical deterioration. (40)

Compensating the high intracavitary pressures, the concentric hypertrophy seems to be an appropriate and beneficial adaptation. Unfortunately, the hypertrophied muscle mass leads to adverse consequences. The myocardial oxygen requirements are elevated, due to the hypertrophied muscle mass, the increased systolic pressure and the prolongation of ejection. In addition there may be an interference with coronary blood flow per gram of muscle even in absence of obstructive coronary artery disease, caused by the abnormally increased pressure compressing the coronary arteries thereby exceeding the coronary perfusion pressure. (41–43)
Furthermore patients with aortic stenosis are susceptible to subendocardial and myocardial ischemia during hemodynamic stress of exercise or tachycardia. Vascular abnormalities inherent in myocardial hypertrophy may impair coronary vasodilatation, limiting the ability to increase coronary blood flow to meet increased metabolic demands. The aortic stenosis itself may cause an imbalance between oxygen supply and demand during hemodynamic stress by decreasing aortic pressure (decreasing coronary perfusion or oxygen supply) and increasing left ventricular pressure (increasing oxygen demand). This maldistribution of coronary blood flow can contribute to systolic or diastolic dysfunction of the left ventricle. (43)
Koyanagi et al. demonstrated in a study with dogs that hypertrophied hearts possess a highly increased sensitivity to ischemic injury, with extended infarcts, mainly in the midwall layer and higher mortality rates (54% vs 17%) than are seen in the absence of hypertrophy. (44)

Aurigemma et al. (45) investigated gender-related differences in left ventricular (LV) and myocardial function by analysis of end-systolic circumferential stress versus shortening relations in 65 patients (29 men and 36 women) with aortic stenosis. When compared to men, women showed higher peak LV pressures (205 ± 27 vs 188 ± 27 mmHg, $p < 0.01$) and higher ejection fractions (66 ± 14% vs 57 ± 18%, $p < 0.05$) despite similar average values for aortic valve area (0.6 ± 3 vs 0.7 ± 4 cm^2). In addition women had smaller LV end-diastolic dimensions (43 ± 8 vs 51 ± 6 mm, $p < 0.01$) and higher relative wall thickness (0.66 ± 0.27 vs 0.50 ± 0.10, $p < 0.01$), whereas 9 women (25%) featured very high values for the diastolic relative wall thickness (exceeding 0.8).
Orsinelli et al. (46) observed the outcome in 54 patients undergoing aortic valve replacement for severe aortic stenosis. The 12 patients who died in hospital had significantly higher relative wall thickness (0.72 ± 0.38 vs 0.56 ± 0.15, $p < 0.04$). Relative wall thickness values higher than 0.66 were associated with a trend towards increased mortality (42% vs 17%, $p = 0.07$) and even more dramatic in women (63% vs 14%, $p = 0.07$).

The relative wall thickness is an indicator for an excessive or inappropriate hypertrophy that is associated with a low systolic wall stress and therefore a high ejection fraction and a high perioperative morbidity and mortality. (45; 46)

Symptoms

Cardinal symptoms like exertional dyspnea, angina pectoris, syncope and ultimately heart failure typically occur at the age 50 - 70 with bicuspid and over 70 with trileaflet aortic valve stenosis. However some patients with severe AS remain asymptomatic, whereas others with only moderate stenosis develop symptoms. (2; 5; 47)

The most common finding in patients with aortic stenosis is fatigue or dyspnea on exertion and the gradual decrease in exercise tolerance. Exertional dyspnea may be due to left ventricular dystolic dysfunction, with an excessive rise in enddiastolic pressure leading to pulmonary congestive, or due to the limited ability to increase cardiac output with a stenotic valve. Late symptoms, like paroxysmal nocturnal dyspnea, exertional dyspnea with orthopnea and pulmonary edema, which represent various degrees of pulmonary venous hypertension, are through interventions nowadays uncommon. (47)

Angina occurs in about two thirds in patients with aortic stenosis. It resembles the angina observed in patients with coronary artery disease and is as well precipitated by exertion and relieved by rest. In contrast to the coronary artery disease angina, the angina in aortic stenosis is not caused by coronary artery obstruction but by the elevated demand for oxygen of the hypertrophied left ventricle and the reduced oxygen delivery caused by the compression of coronary vessels. Very rarely angina results from calcium emboli to the coronary vascular bed. (41 - 43; 47)

Syncope usually arises during exercise. In healthy individuals, cardiac output rises during exercise and total peripheral resistance falls. The narrowed outflow orifice in patients with aortic stenosis fixes the stroke volume on a certain level that usually rises during exercise, the peripheral resistance falls nonetheless, leading to reduced blood pressure and low cerebral perfusion followed by syncope. Other researchers have postulated that the very high intraventricular pressure that develops during exercise in people with aortic stenosis causes a reflex depressor response, in turn causing syncope (vasoplegic syncope). Premonitory exertional hypotension may manifest as graying out or dizziness.

Syncope at rest may be due to transient ventricular fibrillation, which leads to a loss of the atrial contribution to left ventricular filling, consecutive to a harsh decline in cardiac output.

Atrioventricular block caused by extension of the calcification of the valve into the conduction system may be another possibility for syncope in rest. (33; 47)

Gastrointestinal bleeding, often in combination with angiodysplasia (Heyde-Syndrom), may develop in patients with severe aortic stenosis. The high shear forces while passing the stenotic valve lead to proteolysis of the highest-molecular-weight multimers of von Willebrand factor and an increase of proteolytic subunit fragments. These abnormalities correlate with the severity of aortic stenosis and are correctable with an aortic valve replacement. (47; 48)

Diagnosis

Physical examination

The key features of the aortic stenosis in auscultation are the typical crescendo-decrescendo systolic ejection murmur radiating to the neck. In mild disease, the murmur peaks early in systole, S2 is physiologically split, and carotid upstrokes are normal. As aortic stenosis progresses, the murmur becomes louder, peaks progressively later in systole, and is associated with a thrill, due to the progressing calcification S2 may become single, since the stenotic valve neither opens nor closes well. S4 is usually heard in patients in sinus rhythm.

With further worsening of stenosis, the murmur intensity lessens because stroke volume becomes reduced. Carotid upstrokes are diminished in volume and the rate of rise is delayed (pulsus parvus et tardus). In contradistinction, the left-ventricular apical impulse is forceful and slightly enlarged. The discrepancy between a powerful apex beat and diminished carotid pulses is good evidence of an obstruction between the two anatomic structures.

Dynamic auscultation is helpful to further clarify the suspicion on aortic stenosis. The murmur of valvular aortic stenosis is augmented by squatting, which increases stroke volume, and reduced in intensity when standing and during the Valsalva maneuver, due to the reduced venous return. (33; 47)

Echocardiography

Echocardiography has become the key tool for the diagnosis and evaluation of valve disease, and is the primary non-invasive imaging method for valve stenosis assessment. Transthoracic imaging usually is adequate, to evaluate the valve anatomy, the cause of aortic stenosis and the severity of valve calcification. Additionally it is possible to assess the left ventricular wall thickness and function, with calculation of ejection fraction, as well as to measure the aortic root dimensions and detect the presence of associated mitral valve disease.

The antegrade systolic velocity across the narrowed aortic valve, or aortic jet velocity, is measured using continuous-wave Doppler ultrasound. Aortic jet velocity is defined as the highest velocity signal obtained from any window (apical and suprasternal or right parasternal most frequently).

The mean transaortic pressure gradient, which represents the pressure difference between the left ventricular and aorta in systole, can be obtained with the modified Bernoulli equation:

$$\Delta P = 4v^2$$

ΔP is pressure gradient and V is peak transvalvular flow velocity.

Aortic valve area calculation uses the continuity equation, which assumes flow (F) on both sides of the valve is equal ($F_1=F_2$). Flow is defined as area (A) multiplied by velocity (V), so $F_1= v_1 \times A_1= F_2 = v_2 \times A_2$. Here, flow is equal to stroke volume, because V is the velocity-time integral (instead of peak velocity), which gives a mean velocity over the time the flow is taking place (units of v/t are cm/sec/sec, ie, cm). Thus, A×v/t gives $cm^2 \times cm = cm^3$. As flow reaches the narrowed aortic valve, velocity must increase for flow to stay constant. Solving the equation leads to following result:

$$A_2 = A_1 \cdot v_1 / v_2$$

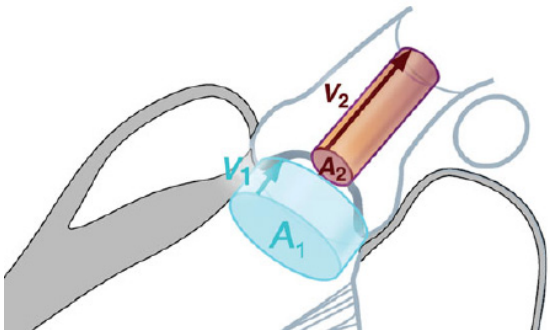

Figure 1 Schematic diagram of the continuity equation. (49)

To calculate the valve area (A_2) following measurements are needed: aortic jet velocity (v_2), left ventricular outflow tract velocity (v_1), and left ventricular outflow tract diameter for calculation of a circular cross sectional area (A_1).

Although echocardiographic and invasive haemodynamic assessment of severity of aortic stenosis are usually in agreement, downstream pressure recovery can alter both methods of gradient measurement. (33; 47; 49)

Stress echocardiography using low-dose dobutamine is indicated for patients with low-flow low-gradient aortic stenosis to distinguish truly severe aortic stenosis from the rare cases of

pseudosevere aortic stenosis. Truly severe aortic stenosis shows only small changes in valve area (increase < 0.2 cm^2) with increasing flow rate but significant increase in gradients (maximum value of mean gradient > 50 mmHg), whereas pseudosevere aortic stenosis shows marked increase in valve area but only minor changes in gradients. In addition, this test may detect the presence of contractile reserve (increase > 20% of stroke volume during low-dose dobutamine test), which has prognostic implications. (2; 50)

Exercise testing should only be performed on asymptomatic individuals with severe aortic stenosis and under close monitoring of blood pressure and electrocardiography. Das et al. noted that more than a third of such patients developed symptoms during exercise. Most probably, these individuals either were denying their symptoms or simply failed to recognise them, and they should be reclassified as symptomatic. Observation of an abnormal hemodynamic response (exercise-induced hypotension or ventricular tachycardia) is considered a poor prognostic finding. (2; 3; 33; 51)

Cardiac catheterisation

Cardiac catheterisation and angiography are recommended before aortic valve replacement to evaluate the status of the coronary arteries. In general the non-invasive haemodynamic valve assessment of the valve is completely adequate. However, when a patient's history, physical examination, and echocardiographic measurements are inconsistent and leave doubt about stenosis severity, a well-performed, invasive haemodynamic study remains the gold standard of diagnosis. (3; 33)

Other diagnostic evaluation

85% patients with severe aortic stenosis present themselves with a left ventricular and around 80% with a left atrial hyperptrophy in the electrocardiogram. The correlation between the absolute electrocardiogram and the severitiy of the obstruction is poor in adults, therefore the absence of left ventricular hypertophy does not exclude an aortic stenosis. In advanced cases, ST-segment depression and T-wave inversion in leads are evident. Abnormal frequency is observed in 15% of aortic stenosis patients. Calcific infiltrates from the aortic valve may lead to various forms of atrioventricular and intraventricular block in 5% of the patients, more common in patients with a mitral annual calcification. (47)

The heart on chest roentgenogram may show no or little overall cardiac enlargement, with a rounding of the left ventricular border and the apex. Substantial hypertrophy is only present in

patients with regurgitation or left ventricular failure. Dilatation of the ascending aorta is common in patients, especially in those with a bicuspid aortic valve. Aortic calcification is usually readily apparent in all patients with a hemodynamically significant aortic stenosis on fluoroscopic examination, cardiac computed tomography or by echocardiography. the left atrium may be slightly enlarged in patients with severe aortic stenosis, and there may be radiological signs of pulmonary venous hypertension. However when left atrial enlargement is marked, the presence of associated mitral valvular disease should be suspected. (47)

The chest computed tomography is useful to clarify aortic valve calcification and to evaluate aortic dilatation found by roentgenogram or echocardiography. Measurement of aortic dimensions at several levels including the sinuses of Valsalva, sinotubular junction and ascending aorta is necessary for clinical decision making and surgical planning. (47)

Cardiac magnetic resonance is useful in assessing left ventricular volume, function, and mass, especially in setting when this information cannot be obtained from echocardiography. (47)

Biomarkers

Brain natriuretic peptide (BNP) seems to be an objective prognostic variable and is thought to be a marker of both hypertrophy and use of preload reserve to maintain compensation. BNP is thought to be a marker of hypertrophy as well as use of preload reserve to maintain function. Therefore several study groups examined brain natriuretic peptide, N-terminal pro BNP (NT-proBNP), and N-terminal atrial natriuretic peptide levels in patients with severe aortic stenosis. Symptomatic patients had higher amounts of BNP or pro-BNP than individuals without symptoms. Asymptomatic patients who developed symptoms during follow-up had higher BNP and NT-proBNP levels at entry compared with those remaining asymptomatic. (33; 53)

Thus, BNP could become a useful marker in predicting onset of symptoms, the presence of renal disease, pulmonary hypertension, and obesity however all interfere with the predictive value of BNP measurement. (33)

Natural history

The asymptomatic aortic stenosis

Asymptomatic patients with aortic stenosis have clinical outcomes similar to age-matched general population. The severity of the outflow tract obstruction gradually increases over 10

to 15 years, so there is a long latent period during which stenosis severity is only mild to moderate. (3; 55)

Cosmi et al. conducted a study with the aim to identify, if aortic valve thickening is a predictor of aortic stenosis. 2131 patients with aortic valve thickening but no obstruction to outflow were analyzed regarding the occurrence of aortic stenosis. During 1 year of echocardiographic follow-up 338 patients (15.9%) developed valve obstruction of any degree (mild, 10.5%; moderate, 2.9%; and severe, 2.5%). However the development of a moderate or severe aortic stenosis emerges at an average of 8 years after the diagnosis of aortic sclerosis. (56)

Once moderate to severe stenosis is present, prognosis remains excellent as long as the patient remains asymptomatic. Varadarajan et al. examined in a retrospective echocardiographic study the survival of 453 patients, who did not undergo aortic valve replacement. The survival rate reflects the progressive nature of the disease (at 1 year 62%, 5 years 32% and 10 years 18%) and the need for close follow-up. (55)
The strongest predictor of progression to symptoms is the Doppler aortic jet velocity. The likelihood of remaining free of symptoms without valve replacement is 84 ± 16% percent at 2 years when jet velocity is less than 3 m/s compared with 66 ± 13% for a velocity of 3.0 to 4.0 m/s, respectively only 21 ± 18% when jet velocity is greater than 4 m/s. The following Cox regression model demonstrates the need for an intensified care for patients with aortic jet velocity greater than 3 m/s. (57)

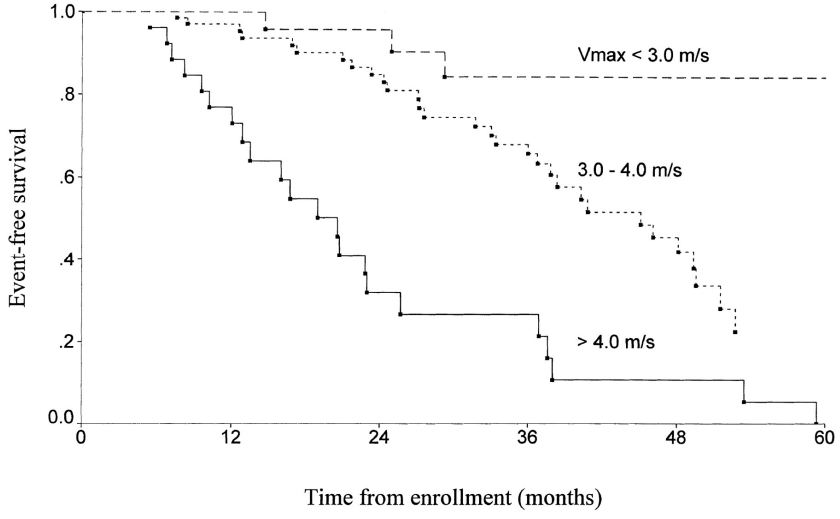

Figure 2 Event free survival of patients in months matched with the aortic jet velocity. (57)

Rosenhek et al. followed 176 asymptomatic patients with mild to moderate aortic stenosis. The degree of valve calcification seemed to be the most powerful predictor of outcome. In adults with moderate to severe calcification of the aortic valve event-free survival at 5 years was 42 ± 7%, compared with 82 ± 5 % in those with little or mild valve calcification.

Patients with higher aortic jet velocity had a higher event rate as well. Event free survival at 5 years for patients with an aortic jet velocity >3 m/s was 55 ± 5 % at 5 years compared to 82 ± 5 % at 5 years for patients with an aortic jet velocity <3 m/s. (58) Retrospective studies reported some cases of sudden death in apparently asymptomatic adults with severe AS. However, more recent prospective studies suggest that sudden death in asymptomatic patients is very unlikely, with an estimated risk of less than 1 percent per year. (3; 59)

The symptomatic aortic stenosis

The retrospective cohorte study (453 patients, follow-up 10 years) from Varadarajan (55) conducted in the Loma Linda University Medical Center in California is the most recent and extensive examination on the topic of the natural history of aortic stenosis.

Severe aortic stenosis was defined as a Doppler estimated aortic valve area of 0.8 cm² or less. 55% patients were younger than 80 years, 52% patients were female and the mean left ventricular ejection fraction was 52 ± 21%. Patients had several relevant comorbidities: congestive heart failure (42%), hypertension (35%), coronary artery disease (34%), diabetes mellitus (14%), renal insufficiency (11%) and history of a stroke (11%). Survival rates were 62% at 1 year, 32% at 5 years and 18% at 10 years.

Treatment with aspirin or statins did not improve survival although many of these patients had coronary artery disease. β-blockers, usually reducing the risk of atrial fibrillation or ventricular arrhythmias, had no impact on the patient survival. Neither the β-blockers nor the angiotensin converting enzyme inhibitors improved survival of the patients with an ejection fraction less than 40%.

Unoperated patients with severe aortic stenosis have an alarming prognosis and it is aggravated in the presence of advanced age (>80 years), LV dysfunction, heart failure, and renal failure. These findings are reflected in the short duration of the mean follow-up (1.5 years), due to the high short-term mortality rate.

Several smaller studies showed a similar dismal outcome:

Horstkotte examined 55 patients with severe stenosis who had refused to undergo aortic valve replacement. The mean survival averaged 23 ± 5 months and the 5-year probability of survival was 18%. All these patients died within 12 years of observation. Mean survival after the occurrence of angina pectoris was 45 ± 13 months, after syncope 27 ± 15 months, and after first occurrence of left heart failure 11 ± 10 months. (60)

Chizner described poor survival of 42 catheterized adult patients with isolated valvular aortic stenosis, who did not undergo early valve replacement. The 32 symptomatic patients were followed until death or for an average of 64.4 months after catheterization. Survival rates from onset of symptoms were 74% at 1 year, 52% at 2 years and 43% at 3 years. (61)

The first study following solely aortic stenosis conducted by Frank in 1973 bore following results. Fifteen adult patients (aged 32 to 59 years) with significant valvular aortic stenosis were followed for up to 11.7 years, or until death. The survival rates were 64% at 3 years, 48% at 5 years and 10% at 10 years. (62)

In a nutshell the development of symptoms, like angina pectoris, syncope, dyspnea or congestive heart failure, in the course of the disease lead to a dramatic decrease of the survival rate of the patients (average survival is 2-3 years). Sudden cardiac death, presumably resulting from arrhythmia, is a frequent cause of death in patients who have previously been symptomatic. (2; 3)

Hemodynamic progression

The rate of hemodynamic progression per year for the individual patient is very unpredictable and variable. Once even moderate stenosis is present (jet velocity > 3.0 m/s), the average rate of annual progression is a decrease in aortic valve area of 0.1 cm^2, an increase in aortic jet velocity of 0.3 m/s and an increase in mean pressure gradient of 7 mmHg. (3; 57)

Therapy

Medical treatment

The progression of degenerative aortic stenosis and artherosclerosis are both an active inflammatory process sharing many risk factors. (8) Therefore cardiac risk factor modifications and general prevention of artherosclerotic risk factors should be recommended,

combined with physical activity and exercise based on the hemodynamic severity of the stenotic lesion. (2; 3)

Several studies investigated the influence of statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) or angiotensin converting enzyme inhibitors on the progression of aortic stenosis.

Rosenhek et al. examined 211 patients with native aortic stenosis (peak velocity > 2.5 m/s), with normal left ventricular function and no other significant valvular lesion. 102 patients received treatment with angiotensin converting enzyme inhibitors, 50 patients were treated with statins, and 32 patients received both. Hemodynamic progression of AS was assessed and related to medical treatment. Annualized increase in peak aortic jet velocity for the entire study group was 0.32 ± 0.44 m/s per year. Patients treated with statins (0.10 ± 0.41 m/s per year) had a significantly lower progression than those who were not (0.39 ± 0.42 m/s per year; $P<0.0001$). Furthermore angiotensin converting enzyme inhibitors, did not significantly affect hemodynamic progression and had no additional effect on aortic stenosis progression when given in combination with statins. (63)

Cowell and colleagues, conducted a randomised trial with 155 people with native aortic stenosis (peak velocity > 2.5 m/s) came to a different result. The study cohort was randomly allocated to either placebo or atorvastatin (80mg) for a treatment duration of at least 2 years. Increases in aortic-jet velocity were 0.199 ± 0.210 m/s per year in the atorvastatin and 0.203 ± 0.208 m/s per year in the placebo group. Interestingly, there was no relationship between serum LDL cholesterol concentrations and the progression of aortic stenosis, nor did high-dose atorvastatin have a demonstrable effect on clinical end points. Therefore intensive lipid-lowering therapy does not halt the progression of calcific aortic stenosis or induce its regression. (64)

The most recent and extensive examiantion on the topic was conducted by Rossebø et al. (SEAS Trial) (65). The randomized, double-blind trial, included 1873 patients with mild to moderate, asymptomatic aortic stenosis (peak velocity > 2.5 m/s - < 4 m/s). After randomization the patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily during a median follow-up time of 52.2 months.

During follow-up, the primary outcome, which was defined as major cardiac events (death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting,

percutaneous coronary intervention and nonhemorrhagic stroke), occurred in 333 patients (35.3%) in the simvastatin–ezetimibe group and in 355 patients (38.2%) in the placebo group (hazard ratio in the simvastatin–ezetimibe group, 0.96; 95% CI, 0.83 to 1.12; p =0.59).

There was no significant difference between the two study groups in the secondary outcome of aortic-valve–related events (aortic-valve replacement, death from cardiovascular causes, and hospitalization for heart failure due to progression of aortic stenosis (hazard ratio, 0.97; 95% CI, 0.83 to 1.14; p = 0.73). Aortic-valve replacement was performed in 267 patients (28.3%) in the simvastatin–ezetimibe group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; p =0.97).

In the placebo group, the mean peak aortic jet velocity was 3.71 ± 0.76 m/s at the end of the study, an increase of 0.62 ± 0.61 m/s. This change was similar to that in the simvastatin–ezetimibe group, in which the velocity was 3.69 ± 0.78 m/s at the end of the study, an increase of 0.61 ± 0.59 m/s (95% CI, −0.06 to 0.05; p =0.83).

Fewer patients had ischemic cardiovascular events in the simvastatin–ezetimibe group (n=148) than in the placebo group (n=187) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; p =0.02), mainly because of the smaller number of patients who underwent coronary-artery bypass grafting. Cancer occurred more frequently in the simvastatin–ezetimibe group (105 vs. 70, p =0.01).

The combination of simvastatin and ezetimibe resulted in an average reduction in LDL cholesterol of at least 50%, as compared with placebo. Despite this favorable effect over a minimum period of 4 years, there was no overall effect on aorticvalve stenosis and no significant overall effect on the composite outcome of combined aorticvalve events and ischemic events in patients with aortic stenosis. In general the therapy reduced the incidence of ischemic cardiovascular events, primarily through reducing the need for a coronary artery bypass graft, but not events related to aortic-valve stenosis. (65)

Both the American Heart Association and the European Society of Cardiology recommend in the guidelines for the management of patients with valvular heart disease an antibiotic prophylaxis in all patients with aortic stenosis for prevention of infective endocarditis and for those with rheumatic aortic stenosis, to prevent a recurrent rheumatic fever. (2; 3)

Patients with associated systemic hypertension should be treated cautiously with diuretics or vasodilators, often angiotensin converting enzyme inhibitors. β-blockers pose the danger of reduced inotropy in an already overloaded ventricle. (2; 33)

Sodium nitropusside rapidly and markedly improves cardiac function in patients with aortic stenosis and decompensated heart failure or pulmonary oedema. It provides a safe and effective bridge to aortic-valve replacement or oral vasodilator therapy in these critically ill patients. (66) Analysis of the mechanism of benefit suggest that primarily an improvement of contractility, rather than a reduction of the peripheral resistance was eligible for the effect. Patients with decompensated aortic stenosis suffer from high left ventricular filling pressure, which compress the endocardium and reduces additional the coronary blood flow, which is already impaired through the existent imbalance of the coronary reserve. It seems that sodium nitropusside reduce filling pressure and augment myocardial blood flow, in turn relieving ischemia and therefore leading to a general improvement of the heart contractility. (67)

Surgical treatment

As depicted in the natural history chapter, patients with symptomatic aortic stenosis, who do not undergo surgery have a dismal prognosis. Therefore early aortic valve replacement should be strongly recommended when symptoms due to severe aortic stenosis are present.

Operative mortality of isolated aortic valve replacement is ~ 3-5% in patients below 70 years and 5-15% in older adults. The following factors increase the risk of operative mortality: older age, associated comorbidities, female gender, higher functional class, emergency operation, LV dysfunction, pulmonary hypertension, coexisting coronary disease, and previous bypass or valve surgery. (2) After successful aortic valve replacement symptoms are less prominent, life quality generals improves and long time survival of operated patients is nearly equal to an age matched population. (68) Risk factors for late death include age, comorbidities, severe functional condition, LV dysfunction, ventricular arrhythmias, and untreated coexisting coronary artery disease. In addition, poor postoperative outcome may result from prosthesis-related complications and sub-optimal prosthetic valve haemodynamic performance. (2)

The salutary results of surgery are partly dependent on left ventricular function. As long as mean gradient is still > 40 mmHg, there is virtually no lower ejection fraction limit for surgery. On the other hand, the management of patients with low-flow, low-gradient aortic stenosis (severely reduced ejection fraction and mean gradient < 40 mmHg) is more controversial. (2)

Subnormal ejection fraction in aortic stenosis stems from afterload excess, contractile dysfunction, or both. (33) When afterload excess is the primary cause, prognosis after aortic

valve replacement is usually good. This procedure relieves the obstruction to outflow, afterload falls, and ejection fraction usually increases strikingly. (69)
However secondary improvement in left ventricular function is uncertain if the primary cause is scarring due to extensive myocardial infarction. Especially when muscle dysfunction prevents cardiac output from generating a mean gradient of more than 30 mmHg, prognosis is greatly impaired. (70) Although such patients have a poor outlook, some do get better after surgery. The best way to predict whether the left ventricular dysfunction is due to a stenotic aortic valve or due to an independent cardiomyopathie is to evaluate the contractile reserve by a dobutamine stress test. Patients whose stroke volume rose by more than 20% during dobutamine infusion greatly benefited from an aortic valve replacement. (33) Conversely, the outcome of patients without contractile reserve is compromised by a high operative mortality despite a trend towards better survival after surgery. (2)

The management of asyptomatic patients with severe stenosis remains still a matter of debate. The decision to operate on asymptomatic patients has to be made very carefully. In most asymptomatic patients, the risk of surgery is greater than the risk of watchful waiting so that management includes patient education, periodic echocardiography, and cardiac risk factor modification. (71)
The European Society of Cardiology recommend in their guidelines on the management of valvular heart disease to operate only in selected asymptomatic patients with a low perioperative risk: (2)

- Patients with depressed LV function due to aortic stenosis
- Patients with echocardiographic predictors of poor outcome (markedly calcified valve and an increase in peak aortic velocity of ≥ 0.3 m/s per year)
- Symptom development in exercise test in physically active patients

Balloon valvuloplasty

Percutaneous balloon aortic valvotomy is a procedure in which one or more balloons are placed across a stenotic valve and inflated to decrease the severity of aortic stenosis. This procedure has a very limited role in older adults and can be considered as a bridge to surgery in haemodynamically unstable patients who are at high risk for surgery or in patients with symptomatic severe aortic stenosis who require urgent major non-cardiac surgery.

The mechanism underlying relief of the stenotic lesion in older adults is fracture of calcific deposits within the valve leaflets and, to a minor degree, stretching of the annulus and separation of the calcified or fused commissures. Immediate hemodynamic results include a moderate reduction in the transvalvular pressure gradient, but the postvalvotomy valve area rarely exceeds 1.0 cm^2. Despite the modest change in valve area, an early symptomatic improvement is usually seen. However, serious acute complications occur with a frequency greater than 10%, and restenosis and clinical deterioration occur within 6 to 12 months in most patients. Therefore, in adults with aortic stenosis, balloon valvotomy is not a substitute for aortic valve replacement. (2; 3)

Multimorbid patients with aortic stenosis

As outlined in the previous chapters aortic valve replacement is the method of choice as therapy of the aortic stenosis. A recent study by Charlson et al. (72) demonstrated that patients aged ≥ 80 years benefit highly, if they receive an aortic valve replacement. However in this age group a fair amount of patients typically suffer from comorbidities like: hypertension, diabetes, chronic renal failure, chronic pulmonary disease, previous cardiac surgery and impaired left ventricular function, which lead, apart from the advanced age, to a significantly heightened perioperativ mortality and morbidity. (73; 74)

Those high risk patients are not viable candidates for traditional surgical aortic valve replacement. A subsequent analysis of the Euro Heart Survey demonstrated that surgery was denied in 33% of elderly patients with severe, symptomatic aortic stenosis. Older age and LV dysfunction were the most striking characteristics of patients who were denied surgery, whereas comorbidity played a less important role. (75)

For those patients rejected for surgical aortic valve replacements, percutaneous aortic valve replacement represents the only curative treatment option.

Percutaneous aortic valve replacement

Even though the first experiments with percutaneous, catheter mounted aortic valve replacement were conducted in the 1970s (76), the general application in humans was postponed due to technical limitations.

The rise of stent technology allowed the first-in-man implantation of a percutaneous catheter mounted valve in pulmonary position in the year 2000 by Bonhoeffer and colleagues. (77) In 2002 Cribier et al. performed the first implantation of a balloon expandable aortic valve prosthesis as a last-resort, potentially lifesaving intervention that might also bridge to surgical valve replacement, in a 57-year-old man with severe calcific aortic stenosis, cardiogenic shock and subacute leg ischemia. (78)

Technical aspects

Currently there are two systems for percutaneous aortic valve replacement in clinical evaluation: the balloon expandable SAPIEN™ aortic valve bioprosthesis (Edwards Lifesciences, Irvine, USA), and the self-expanding CoreValve bioprosthesis (Medtronic CoreValve, Irvine, USA).

The balloon expandable prosthesis

The Edwards SAPIEN™ valve (Edwards Lifesciences Inc) consists of a tubular, slotted, balloon expandable, stainless steel stent with an attached bovine pericardial trileaflet valve. A pericardial skirt covers the left ventricular portion of the prosthesis. A mechanical crimping device is used to attach the prosthesis onto a dedicated valvuloplasty balloon catheter. The valve is currently manufactured with a 23 mm and 26 mm diameter, requiring a 22 F or a 24 F catheter system for delivery.

During prosthesis implantation, rapid right ventricular pacing is used to minimize pulsatile transvalvular flow, which would otherwise lead to dislocation of the inflated deployment balloon. (79; 80)

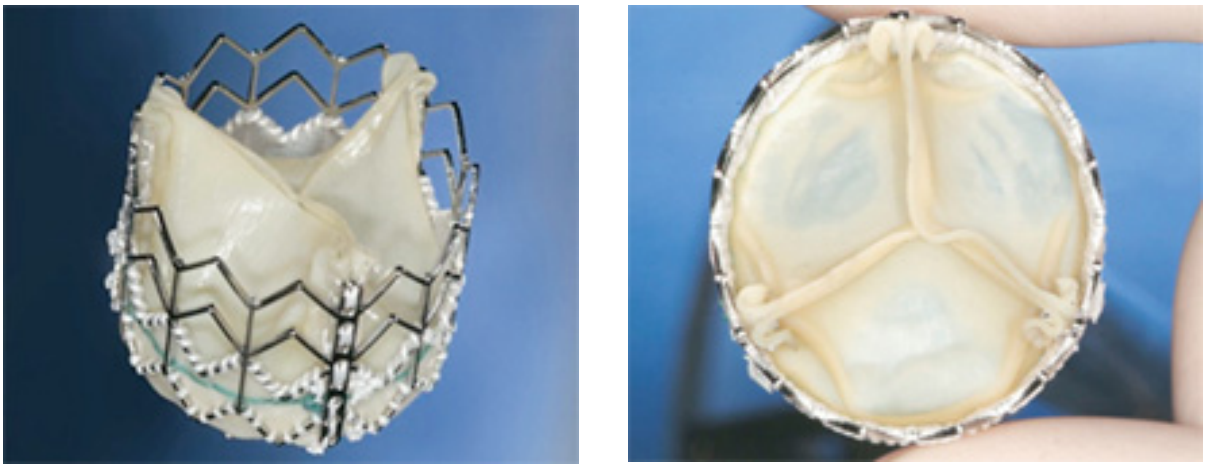

Figure 3 Profile of the Edwards SAPIEN™ transcatheter aortic prosthesis. (80)

The self-expanding prosthesis

The CoreValve aortic valve prosthesis consists of a trileaflet bioprosthetic porcine pericardial tissue valve that is mounted and sutured in a self-expanding nitinol frame (stent). The prosthetic frame is manufactured by laser cutting of a nitinol metal tube with a length of 50 mm. The lower portion of the prosthesis has high radial force to expand and exclude the calcified leaflets and to avoid recoil, the middle portion carries the valve and is constrained to avoid obstruction of the coronary arteries, and the upper portion is flared to fixate the stent in the ascending aorta and to provide longitudinal stability. The current third-generation device has either a diameter of 26 mm or 29 mm, both requiring an 18 F delivery catheter system.
Due to the special design and the gradual release of the prosthesis, rapid right ventricular pacing is not necessary during deployment. (80–82)

Figure 4 Profile of the CoreValve transcatheter aortic prosthesis.

There are three main approaches for this intervention: anterograde transseptal, retrograde and minimally invasive transapical.

Anterograde transseptal approach

Cribier and colleagues used this method in 2002 for the first-in-man percutaneous aortic valve implantation. The anterograde transseptal approach is a challenging technique. A catheter from the left femoral artery is used for continuous blood pressure monitoring, and the right femoral vein is used for valve prosthesis insertion. As a first step the physician conducting the catheterization has to place a guide wire from the femoral vein to the right atrium, via transseptal puncture into the left atrium, advancing through the mitral valve into the left ventricle, crossing the aortic valve and descending the aorta until the wire is externalized through the left femoral artery using a catheter snare. In a second step the transseptal puncture is balloon dilated, as well as the stenotic valve. A new balloon catheter with a mounted valve is introduced, following the guide wire to the stenotic native valve. To decrease aortic blood flow and prevent the risk of valve prosthesis migration during the delivery process rapid cardiac pacing (200 to 220 ppm) of the right ventricle is performed. The delivery balloon and the guidewire are withdrawn immediately after implantation of the valve. (78; 83)

Due to the risk of damaging the heart – potentially leading to mitral regurgitation, hemodynamic instability or pericardial tamponade – and the high risk of atrial and ventricular arrhythmias, the anterograde approach is nowadays only used if there are contraindications for the retrograde or transapical approach. (79; 84)

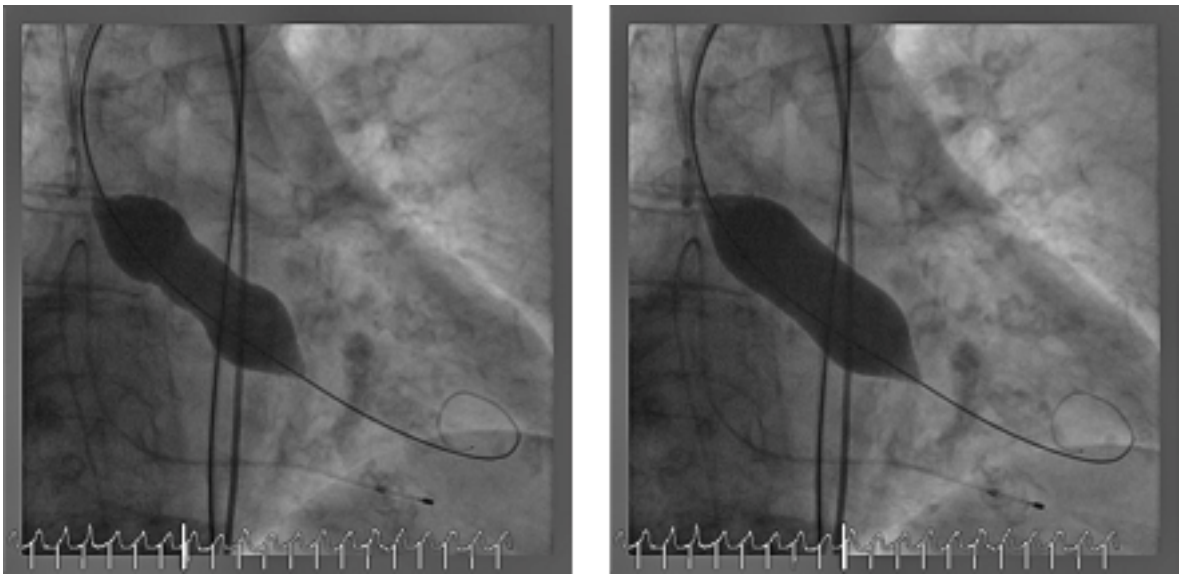

Figure 5 Balloon valvuloplasty: balloon notched by the calcific AV (left) and fully inflated (right).

Retrograde approach

Hanzel et al. performed the first retrograde approach, which is similar to other cardiac interventions and seems to be a less complicated method of deploying the device. (84)

In most patients a percutaneous approach is possible from the femoral artery. Alternatively, the CoreValve prosthesis can also be inserted via the subclavian artery.

After conventional valvuloplasty, a special steerable deflection catheter (Edwards SAPIEN™ valve) or a passive catheter (CoreValve) is used to advance the prosthesis through the (tortuous) aorta and the aortic arch.

The prosthesis typically enters the ascending aorta along its greater curvature, with the guidewire lying within the aortic valve commissure. Crossing the native valve with the prosthesis may require active manipulation of the deflection catheter. (79) Edwards SAPIEN™ valve requires rapid cardiac pacing to release the valve prosthesis in the correct position.

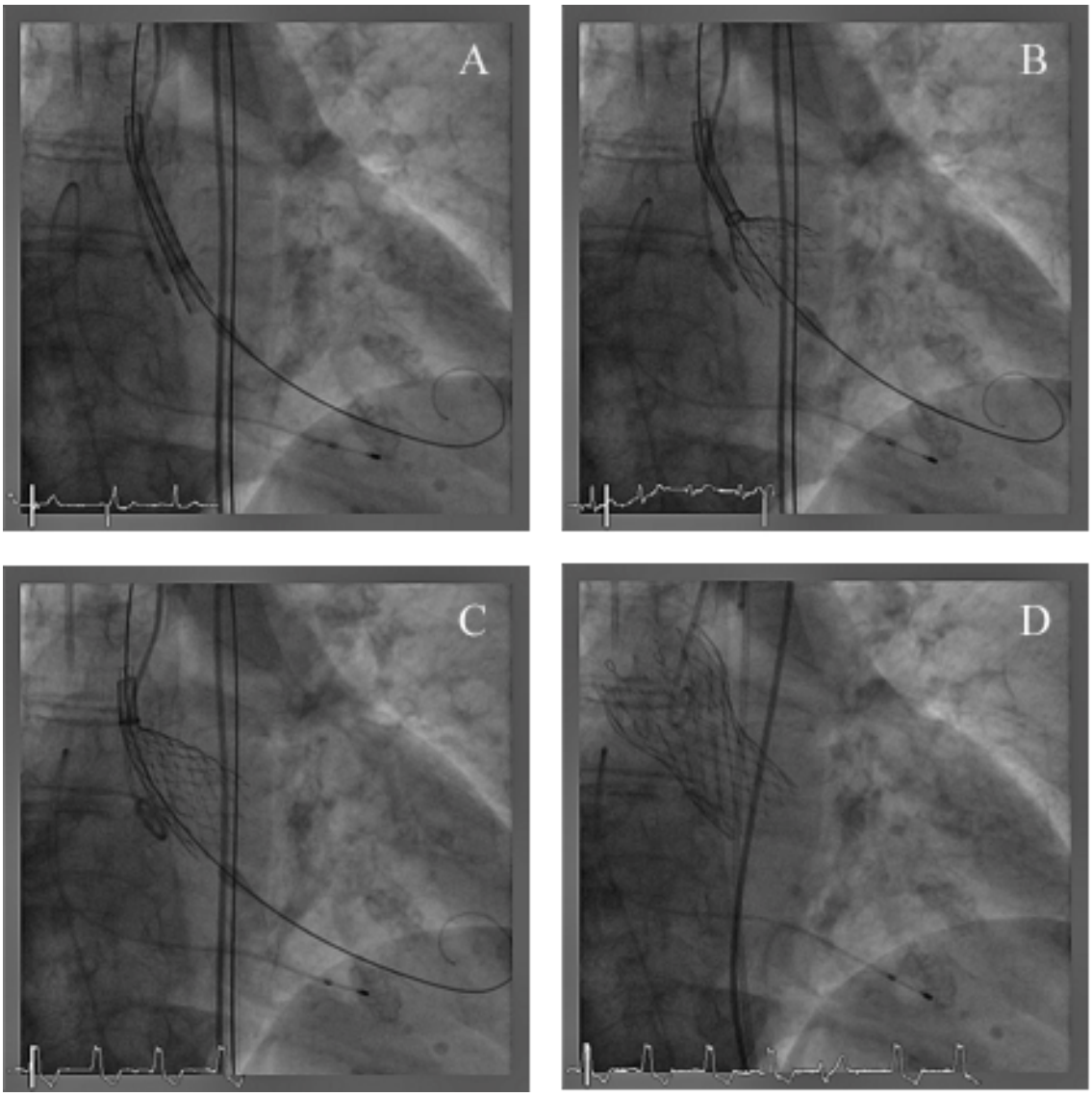

Figure 6 Step-by-step release of the CoreValve bioprosthesis (A – D).

Transapical approach

A minimally invasive procedure, using the Edwards SAPIEN™ valve, is the transapical approach, for patients, who tolerate the stress of general anesthesia and mechanical ventilation. The transapical approach is an alternative for patients with an unfavorable course of the vessel or a minor diameter of the ilio-femoral arteries.

A left anterolateral intercostal incision is used to expose the left ventricular apex. Direct needle puncture of the apex allows introduction of a hemostatic sheath into the left ventricle. The prosthetic valve and balloon catheter are passed over a wire into the left ventricle. Positioning within the aortic annulus is confirmed by fluoroscopy, aortography, and transesophageal echocardiography. Rapid ventricular pacing is used to reduce cardiac output while the balloon is inflated, deploying the prosthesis within the annulus. After deployment, valve function is assessed by echocardiography and angiography. After removal of the left ventricular sheath, hemostasis is secured with previously placed pledgeted sutures. The pericardium is approximated to prevent myocardial herniation and to allow drainage. The remaining layers are sutured, after a left chest tube is placed. (85)

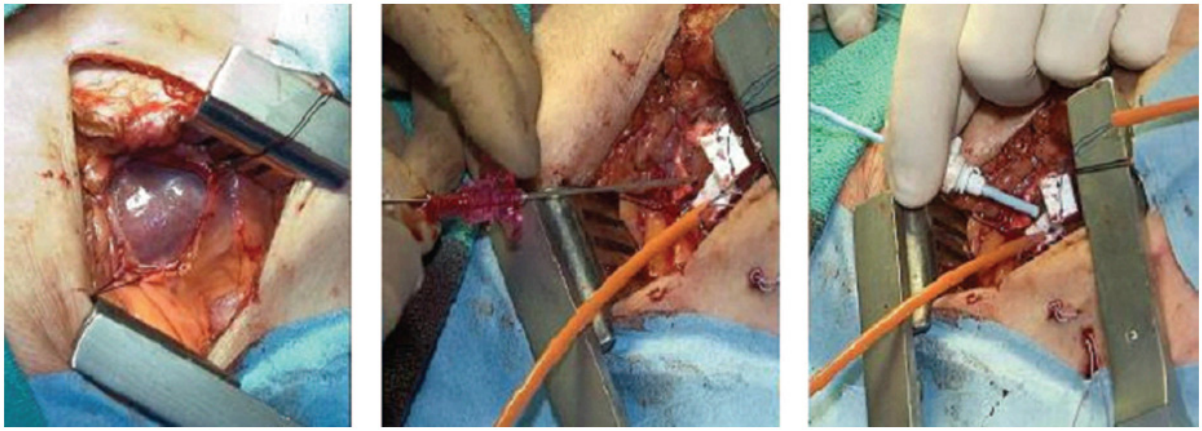

Figure 7 From left to right: An intercostal incision exposes the left ventricular apex. Direct needle puncture is used to access the left ventricle. A standard sheath is used to gain access to the aortic valve. (85)

Outcomes after percutaneous aortic valve replacement

Edwards SAPIEN™ valve

Retrograde approach

The series of retrograde implantation published by Webb et al. (n=50) showed initial procedural success of 78%, which increased to 96% after the first 25 cases. Additionally,

malposition and intraprocedural mortality fell as well, reflecting an important learning curve. (86). In these 50 patients the overall intraprocedural mortality was 2% (one patient), further 5 patients died in the first 30 days, therefore the observed 30-day mortality was lower than the expected 30-day mortality (12% vs 28% calculated by the EuroSCORE). After 6 months the overall survival was 79%.

Transthoracic echocardiography documented an immediate improvement in left ventricular ejection fraction (EF 53 ± 15 vs. 57 ± 13%), an increase in estimated aortic valve area (AVA 0.6 ± 0.2 vs. 1.7 ± 0.4 cm^2) and a reduction in transaortic mean pressure gradient (MPG 46 ± 17 vs. 11 ± 5 mmHg). These improvements are maintained up to 1 year. At median follow-up, there was no evidence of valve deterioration, migration or valvular insufficiency. Moderate perivalvular leaks were seen in 3 cases at 1 month. Perivalvular aortic insufficiency was mild, clinically of no consequence, and stable during follow-up in the majority of the patients.

The main complications were stroke (4%), complete atrioventricular block (4%), pericardial tamponade (2%) and myocardial infarction (2%). (86)

Data from the SOURCE registry (Edwards SAPIEN™ Aortic Bioprothesis European Outcome Registry) show an initial 95% implant success and a 30-day survival of 93.6%. The improvement in the effective orifice area, left ventricular ejection fraction and transaortic MPG are comparable to the previously reported results. Minimal perivalvular aortic insufficiency could be seen in 65% and mild in 26% of the patients.

Transcatheter AVR was aborted in 2.3% primarily because of failed arterial access and inability to cross the valve. Intraprocedural death was 0.3%, 30-day mortality was 6.4%, cerebrovascular events occurred in 3.4%, and vascular complications occurred in 7.4%. Vascular complications increase mortality considerably, suggesting careful patient selection. (80)

Apical approach

In 2006 Lichtenstein et al. (85) published the first feasibility study on the transapical approach in a group of 7 patients. Initial valve implantation was successful in all of them, and there were no procedural deaths. Transvalvular gradient and aortic valve area improvement was seen in all patients, and the results were consistent with those found after retrograde implantation. Observed 30-day mortality was lower than the expected mortality (14% vs. 35% predicted by EuroSCORE) (85)

At the Transcatheter Cardiovascular Therapeutics Congress 2008 Walther presented the interim analysis of data from a large series (n=168) of high-risk patients treated with transapical aortic valve replacement in the TRAVERCE (Trans-Apical surgical Delivery of the Cribier-Edwards Aortic Bioprothesis Clinical Feasibility) study. (87)

Correct placement was seen in 92.8% of the cases, and 7.1% had to be converted to open aortic valve replacement due to aortic insufficiency, valve malposition or valve migration. There were no intraprocedural deaths, 25 patients (14.9%) died in the first 30 days. The overall 6-month survival was 70%. The improvement in left ventricular ejection fraction, aortic valve area (AVA 0.6 vs. 1.5 cm^2) and mean aortic transvalvular pressure gradient (MPG 43 vs. 8 mmHg) was maintained during follow-up.

The main complications were cerebrovascular events, arrhythmias, and partial coronary occlusion in 2.9%, 2.4% and 1.8%, respectively. Ventricular bleeding at the puncture site was seen in 4.8%. Placement of a second valve (valve in valve) was required in 3% to decrease the aortic insufficiency or correct valve malposition. Furthermore, a learning curve is described, resulting in better outcomes after the first 120 patients. (87)

Patients who require the transapical approach have a higher incidence of peripheral vascular disease, which is a marker of worse long-term outcome. Although in its early stage, transapical aortic valve replacement has the potential of becoming a new option for the treatment of high-risk patients, who have a “porcelain aorta” or peripheral vascular disease that limits their candidacy for retrograde aortic valve replacement. (80)

CoreValve

The largest report covering the procedural performance and 30-day outcomes using the 18 F CoreValve Revalving System was published by Piazza et al. (88). From April 2007 to April 2008, 646 patients with symptomatic severe aortic stenosis and a mean age of 81 ± 6.6 years, mean aortic valve area 0.6 ± 0.2 cm^2, and logistic EuroSCORE of 23.1 ± 13.8% were treated with percutaneous aortic valve replacement using the CoreValve revalving system.

The rate of procedural success was 97%. The procedural mortality rate was 1.5%. At 30 days, the all-cause mortality rate (i.e, including procedural) was 8% and the combined rate of death, stroke and myocardial infarction was 9.3%.

After valve implantation, the mean transaortic pressure gradient decreased from 49.4 ± 13.9 to 3 ± 2 mmHg. All patients had paravalvular aortic regurgitation grade 2 or lower. Major complications were myocardial infarction (0.6%), aortic root dissection (0.6%), left or right ventricular perforation (1.7%), cardiac tamponade (1.4%), permanent pacemaker implantation

due to complete atrioventricular block (9.3%) and neurological events (1.9%). From the total 12 stroke events 4 were diagnosed within 24 hours after the procedure, a further 8 "delayed strokes" were detected from 24 hours up to 9 days after intervention. (88)

A study (n=80) conducted at the Division of Cardiology at the Medical University Graz, with the aim to evaluate the 30-day and one-year outcomes after percutaneous aortic valve replacement in patients with symptomatic severe AS and a logistic EuroSCORE >20%, revealed similar results: (89)

Acute procedural success rate was 98.7%. The echocardiographic follow-up 30 days after device implantation revealed a significant reduction of mean aortic transvalvular pressure gradient (MPG 59 ± 16 vs. 11 ± 3 mmHg) and a significant increase of calculated aortic valve area (AVA 0.5 ± 0.1 vs. 1.4 ± 0.2 cm²).

Aortic regurgitation was trivial or mild in 73 patients and moderate in seven patients (8.7%). Permanent pacemaker implantation was necessary in five patients (6.2%) due to complete atrioventricular block. Major complications were myocardial infarction (1.2%), stroke (2.5%) and pericardial tamponade (2.5%). Six patients (7.5%) died within the first 30 days, another nine patients (11.2%) deceased up to twelve months after PAVR. There was no device-related mortality. At one-year follow-up, the reduction of transvalvular pressure gradients and increase of valve area were maintained and not significantly different from 30-day results (MPG 10 ± 4 mmHg, and AVA 1.5 ± 0.4 cm²). (89)

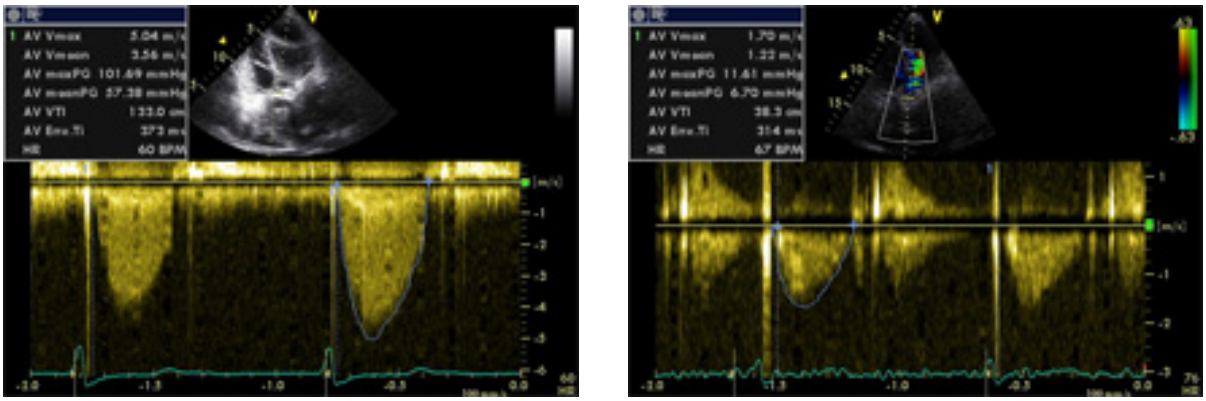

Figure 8 Aortic transvalvular flow (CW Doppler) in an 82 y/o patient with severe aortic stenosis before (left) and one year after (right) PAVR. (89)

Assessment of microembolic cerebral lesions by cerebral MRI

Purpose

Due to the technical aspects of PAVR, a considerable risk of transient ischemic attack or embolic stroke was initially expected. Actually, symptomatic neurological deficits occurred less frequently, ranging from 0.6% (n=646) (88), 2.5% (n=80) (89) to 10% (n=86) (90). This study aimed to assess frequency and extent of subclinical microembolic cerebral lesions after PAVR by comparing pre- and postinterventional diffusion weighted magnetic resonance images (DW MRI).

Patients and Methods

Study Population

From July 2008 to November 2009, 46 patients with symptomatic severe aortic stenosis (15 male, 31 female; mean age 81 ± 5 years) were prospectively and consecutively enrolled in the present study, after informed consent had been obtained. All patients were scheduled for percutaneous aortic valve replacement due to their increased risk of demise with the conventional surgical approach or when patients strictly refused surgical valve replacement.
Exclusion criteria were contraindications for MRI and inability to give written informed consent. 37 patients were scheduled for cerebral diffusion-weighted magnetic resonance imaging (DW MRI) two days before and up to six days after PAVR. Nine patients were not eligible due to pacemaker implantation prior to enrolment. 25 patients underwent both pre- and postinterventional DW MRI, while twelve patients could not undergo postinterventional MRI and had to be excluded from analysis (need for permanent pacemaker implantation, n=2; critical status, n=5; MRI not available, n=5).

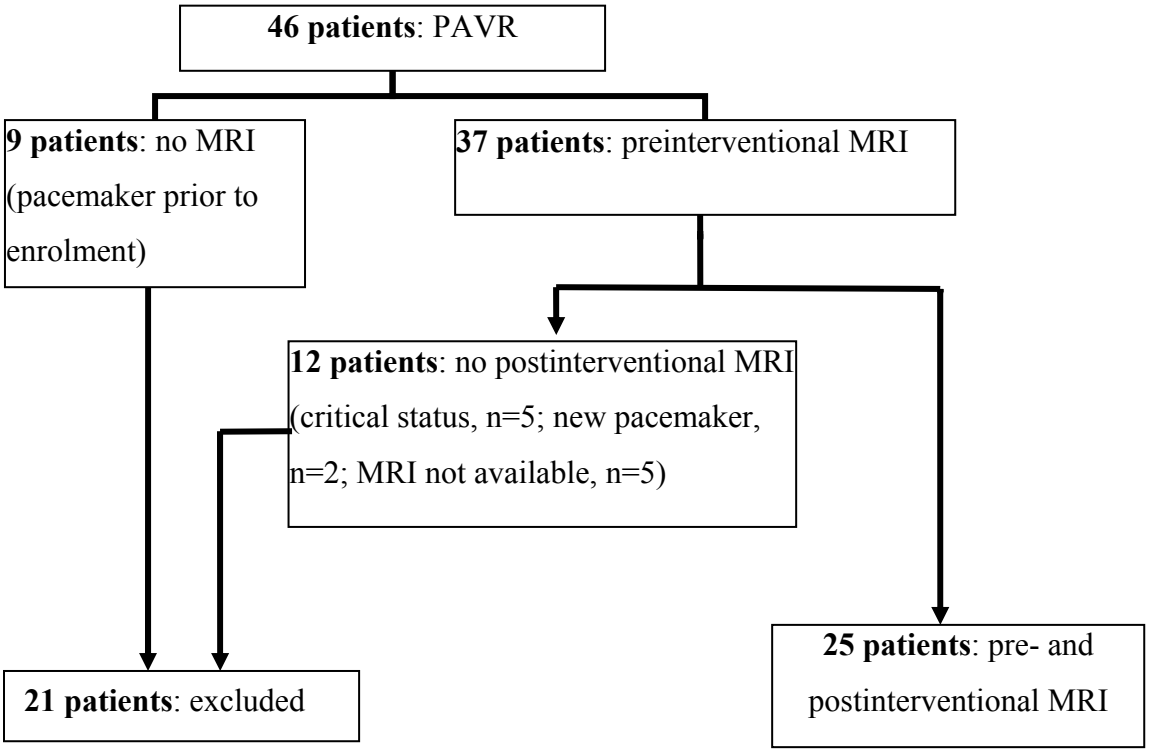

Figure 9 Patient flow chart

Percutaneous aortic valve replacement

All patients were examined clinically and assessed for any history of previous cerebral embolism. Transthoracic echocardiography, 12-lead surface ECG, and coronary angiography were performed in all patients. Selection of the prosthesis size depended on measurement of the aortic annulus diameter obtained by echocardiography, aortography or multi-slice computed tomography.

The procedure was performed by one single expert interventional cardiologist in the catheterization laboratory via a bifemoral percutaneous approach under local anesthesia and analgesic sedation without surgical cut-down and hemodynamic support. After balloon valvuloplasty (balloon size 22 mm or 25 mm), the self-expanding CoreValve prosthesis (diameter 26 mm or 29 mm) was implanted using the current 18 F delivery catheter system. Closure of the femoral artery was performed with the aid of a "pre-closing" device (10 F Prostar XL). Peak and mean pressure gradients were recorded before and after implantation of the device.

The pre-medication regimen consisted of aspirin 100 mg once daily and clopidogrel 75 mg once daily each for three days prior intervention or a clopidogrel loading dose of 300 mg on the day of intervention. Furthermore, one hour prior to the procedure, prophylactic antibiotic

therapy (cefuroxim 1.5g) was administered according to local practice guidelines. During the procedure, a weight-adjusted dose of heparin was given with a target activated clotting time (ACT) of approximately 250 – 300 seconds for the duration of the intervention. Post implantation, a dual antiplatelet strategy of aspirin 100 mg and clopidogrel 75 mg daily for 6 months, followed by aspirin permanently was prescribed.

Magnetic resonance imaging

MRI was done within 50 hours before and up to 144 hours after PAVR, depending on the clinical status of the elderly patients. MRI examinations were performed with an 1.5 Tesla system (Siemens Magnetom Espree). The imaging protocol included a diffusion weighted single-shot spin echo echoplanar sequence acquired in the AC-PC (anterior commissure-posterior commissure) plane with 25 contiguous sections (diffusion gradient b values of 0 and 1000 s/mm², repetition time [TR] 5000 ms, echo time [TE] 114 ms, slice thickness 6 mm with no gap, matrix of 192x100 pixels, and field of view of 230 mm); fluid-attenuated inversion recovery (FLAIR; TR/TE 9770/99 ms, inversion time 2200 ms); and T2-weighted turbo spin echo sequences (TR/TE 4500/85 ms). For DW MRI, the diffusion gradients were successively and separately applied in 3 orthogonal directions for a total acquisition time of 97 seconds. Trace images were then generated and apparent diffusion coefficient maps calculated with a dedicated software tool (Syngo; Siemens). The image analysis was performed independently by two experienced neuroradiologists who were blinded to the clinical data and were unaware of the technical aspects of the percutaneous intervention. For analysis of diffusion weighted MRI, the neuroradiologists were asked to determine the presence, size, number, and vascular distribution of any focal diffusion abnormalities (bright lesions) in a pattern consistent with embolic lesions.

The following score was used to asses the differences between the pre- and postinterventional MRI. Bright lesion was determined as an area with a diameter smaller than 1 cm and cortical infarction was defined as an area with a diameter bigger than 1 cm.

Classification	Difference to preinterventional MRI
0	no difference
I	1 – 3 bright lesions
II	4 – 7 bright lesions
III	≥ 8 bright lesions or cortical infarction

Table 2 Classification used to stage differences in the postinterventional diffusion weighted MRI

Statistical analysis

Baseline characteristics of the study population are presented as counts and percents for categorial variables and as mean ± SD for continuous variables. The number of lesions in our population of patients was examined by two independent neuroradiologists. A paired sample test was used to test the significance of the newly observed bright lesions. The statistical analyses were performed using webbased Citrix SPSS 17.0.0 program.

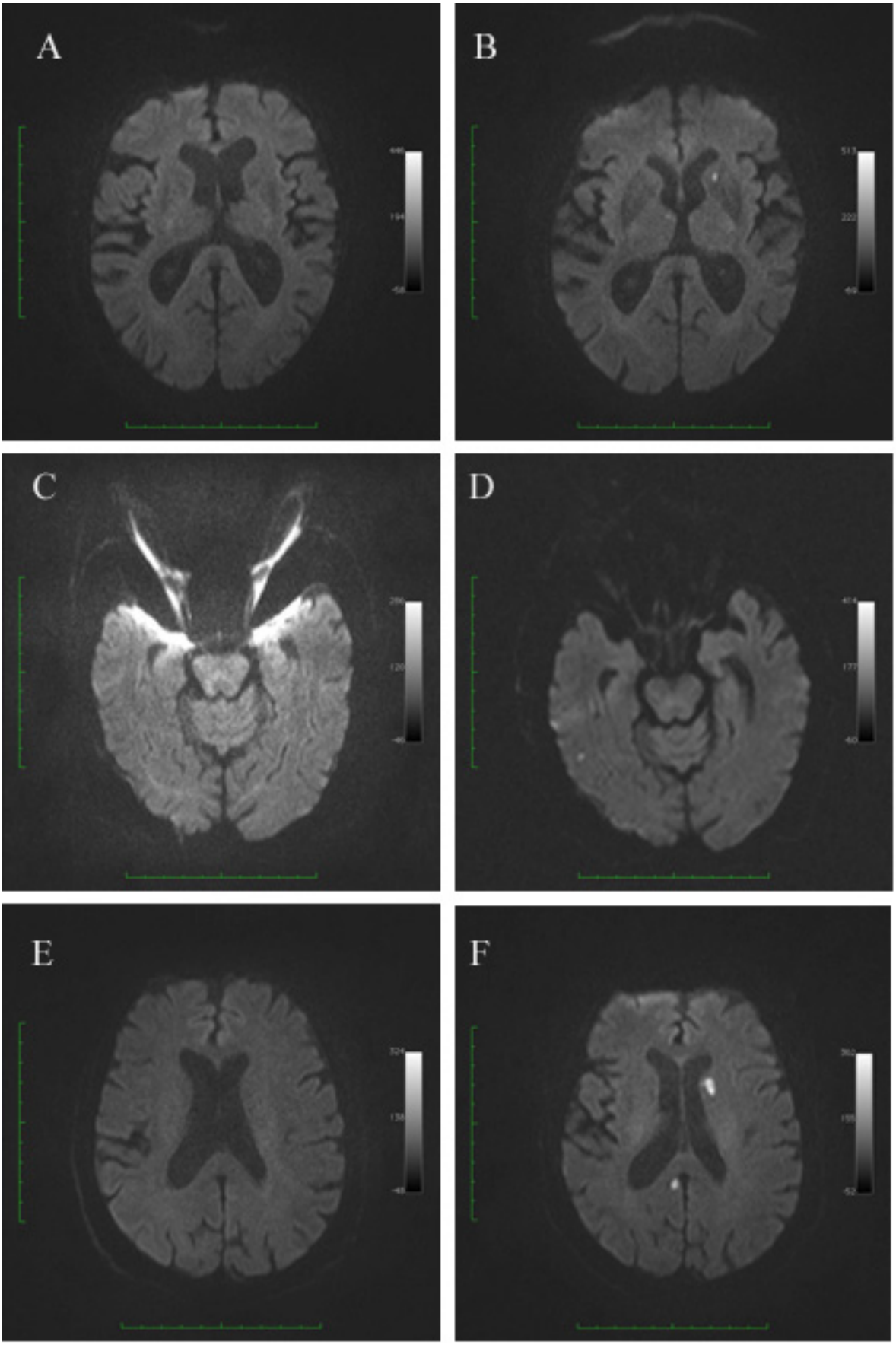

Figure 10 Pre- (A,C,E) and postinterventional (B, D, F) DW MRI. Classification from top to bottom I. II and III accordingly.

Results

Baseline characteristics of the patients, who underwent pre- and postinterventional MRI examinations, are listed in the table below:

No. of patients	25
Male	5 (20%)
Age, [years]	81 ± 5
Logistic EuroSCORE, [%]	12 ± 8
Aortic Vmax before intervention, [m/s]	4.5 ± 0.82
Aortic Vmax after intervention, [m/s]	2 ± 0.47
AVA before intervention, [cm²]	0.52 ± 0.15
AV mean pressure gradient before, [mmHg]	46.98 ± 19.78
AV mean pressure gradient after, [mmHg]	9.56 ± 3.91
EF before intervention: normal (>55%)	16 (64%)
slightly impaired (45-54%)	3 (12%)
moderately impaired (30-44%)	3 (12%)
severely impaired (<30%)	3 (12%)

Table 3 Patient baseline characteristics with 2 diffusion weighted MRI examinations

The patients underwent the first cerebral DW MRI one to two days before intervention and the second DW MRI up to six days after intervention. No change in neurological status was documented in any patient before, during and after PAVR until discharge from hospital. All patients underwent the procedure with successful retrograde implantation of the CoreValve prosthesis (diameter 26 mm, n=12; diameter 29 mm, n=13). Valvuloplasty was performed with a 22 mm balloon (n=12) or a 25 mm balloon (n=12). One single patient did not need a valvuloplasty due to an off-label valve-in-valve implantation.

23 of the 25 patients (92%), who underwent two cerebral DW MRI examinations, showed newly acquired bright lesions ($p < 0.001$).

New bright lesions in comparison to preinterventional cerebral DW MRI	
0	2 (8%)
1 – 3	9 (36%)
4 – 7	8 (32%)
≥ 8 or cortical infarction	6 (24%)

Table 4 Classification and frequency of the newly acquired bright lesions

Further subgroup analysis with a Pearson correlation showed a negative correlation between the amount of bright lesions and the EuroSCORE (-0.552; $p < 0.05$): The higher the amount of newly acquired lesions, the lower the EuroSCORE. Furthermore, there was a positive correlation between the amount of bright lesions and the ejection fraction (-0.68; $p < 0.01$): The higher the amount of newly acquired lesions, the better the ejection fraction.

Discussion

This study demonstrates clearly that the risk of microembolisation in the course of PAVR is very high. The postinterventional DW MRI examination revealed newly acquired bright lesions in 92% of the patients who underwent PAVR. Fortunately, these microinfarctions remained subclinical without any neurological symptoms or deficits, thus not influencing the clinical outcome. This result consolidates the position of the PAVR as a treatment option for high risk patients with severe aortic stenosis, who are not suitable candidates for surgical aortic valve replacement.

A clear limitation of this study is the small patient sample size. In particular, the results of the subgroup analysis are rather hints than facts and are in need of further and extended research. Another issue that could not be examined due to the study design is which part of the intervention (balloon valvuloplasty, crossing the aortic arch with the delivery catheter, expanding/releasing and implanting the valve) leads to the highest burden of microembolisations. This information could be obtained by an intrainterventional transcranial Doppler measurement of typical microembolic signals during the different stages of the intervention.

Additional studies in a larger patient cohort are required to identify special subgroups, who are at increased risk of cerebral embolisation during the procedure.

Conclusion

PAVR with the self-expanding CoreValve bioprosthesis is an emerging alternative treatment option for high-risk patients with symptomatic severe AS. Albeit risk of stroke is low, the vast majority of patients show newly acquired bright lesions in DW MRI compatible with subclinical cerebral embolisation.

Appendix

Glossary and abbreviations

AC-PC	anterior commissure-posterior commissure
ACT	activated clotting time
AS	aortic stenosis
AVA	aortic valve area
aVIC	activated valvular interstitial cell
AVR	aortic valve replacement
BNP	brain natriuretic peptide
BPG	osteocalcin
BSA	body surface area
DW MRI	diffusion-weighted magnetic resonance imaging
ECG	electrocardiogram
ECM	extracellular matrix
EF	ejection fraction
FLAIR	fluid-attenuated inversion recovery
HDL	high density lipoproteins
IFN-γ	interferon γ
IL-4	interleukin 4
LDL	low density lipoproteins
LTA	lipoteichoic acid
LV	left venricular
MGP	γ-carboxyglutamic acid protein
MMP	matrix metalloproteinase
MPG	mean (aortic transvalvular) pressure gradient
NMP	non-collagenous matrix proteins
NT-proBNP	N-terminal pro BNP
obVIC	osteoblastic valvular interstitial cell

PAVR	percutaneous aortic valve replacement
ppm	paces per minute
qVIC	quiescent valvular interstitial cell
Runx2	runt-related transcription factor 2
S2	2nd heartsound
S4	4th heartsound
SPARC	osteonectin; secreted protein, acidic and rich in cysteine
TE	echo time
TGF-β	transforming growth factor β
Tie-2	tyrosine kinase with immunoglobulin-like and EGF-like domains-2
TIMP	tissue inhibitors of matrix metalloproteinase
TNF-α	tumor necrosis factor-α
TR	repetition time
VEGF R-1/2	vascular endothelial growth factor receptor 1/2
VEGF-A	vascular endothelial growth factor A
VIC	valvular interstitial cell
VSMC	vascular smooth muscle cell
αSMA	alpha-smooth muscle actin

List of figures

Figures - unless otherwise stated - by courtesy of Medical University Graz.

List of tables

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Curriculum vitae

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Ausbildung

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10/2002 - 08/2004	**Medizinische Universität Wien** Studium der Humanmedizin	
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09/1994 - 06/2002	**Öffentliches Gymnasium der Stiftung Theresianische Akademie Wien** (Theresianum, Gymnasium mit dritter lebender Fremdsprache)	

Berufserfahrung & Praktika

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10 und 11/2009	**Univ. Klinik der TU Dresden, Herzzentrum** Internistische Fächergruppe für das praktische Jahr Tätigkeiten: Aufnahme von Patienten, Assistenz in den Funktionseinheiten und im Ambulanzbetrieb, tägliche Stationsarbeiten (Normalstation und Intensivstation)	**Dresden**
04 bis 07/2009	**LKH Villach / Warmbad Villach, SKA für Orthopädie** Chirurgische Fächergruppe für das praktische Jahr Tätigkeiten: OP-Assistenz, Aufnahme von Patienten, Ambulanzbetrieb, tägliche Stationsarbeiten	**Villach**
03/2009	**Univ. Klinik Graz, Universitätsklinik für Psychiatrie** Kleine Fächergruppe für das praktische Jahr Tätigkeiten: Aufnahme von Patienten, Explorationen, Assistenz bei EKT, tägliche Stationsarbeiten,	**Graz**
08/2008	**AKH Wien, Universitätsklinik für Herzchirurgie**	**Wien**

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04/2007	**Univ. Klinik Graz, Universitätsklinik für Endokrinologie und Nuklearmedizin** Famulatur Tätigkeiten: stationäre Aufnahmen, Diabetes Schulungen, tägliche Stationsarbeiten	**Graz**
seit 06/2007	**Prometus Verlag** Freier medizinischer Journalist, Redaktion Tätigkeit: Mitarbeit in der Redaktion, Verfassen von Artikeln und Interviews für die Fachzeitschriften „Arzt+Patient“, „Arzt+Kind“, „Der Rheumatologe“ und „Der Internist“	**Graz**
02/2007	**Landesklinikum Graz West, pulmologische Tagesklinik** Famulatur Tätigkeiten: stationäre Aufnahmen, Assistenz bei Bronchoskopie, Lungenfunktion und Provokationstests, C/P-Röntgen und TCT-Befundung, tägliche Stationsarbeiten	**Graz**
08/2006	**Hanusch Krankenhaus, Kardiologie** Famulatur Tätigkeiten: stationäre Aufnahmen, Assistenz bei ärztlichen Tätigkeiten, EKG-Befundung, tägliche Stationsarbeiten	**Wien**
10/2002 bis 08/2004	**Arztpraxis, Kardiologie und Pulmologie** Geringfügige Beschäftigung Tätigkeiten: Organisation und EDV-Betreuung, Assistenz bei ambulanten Sprechstunden, Lungenfunktion und EKG	**Wien**

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